Pharmacogenomics in Clinical Drug Development and Potential for Alopecia Areata

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Alopecia areata, alopecia totalis, and alopecia universalis likely represent a constellation of related diseases with similar, yet distinct heritability markers. There is currently no known curative therapy that works universally for all patients. Pharmacogenomic research enables the pharmaceutical industry to understand variability of patient responses to drugs during clinical drug development and during post-marketing surveillance. Understanding the genetic basis for patient response/non-response can enable the development of individualized therapies for those patients with an inherited basis for altered response to drug therapy. There are multiple examples of drugs that now contain a recommendation for genetic testing before dosing in their drug labels, directing clinicians to obtain genetic information for each individual patient in order to help direct drug therapy.

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Genetic variation in individual patients participating in clinical drug development trials influences patient response to therapy. The pharmaceutical industry uses pharmacogenetic assessment of patients participating in clinical trials to understand if subpopulations of responders that emerge in large patient populations are linked to genetic traits that can be easily assessed before drug treatment (Grecco *et al.*, 2012; Bienfait *et al.*, 2013; Warner *et al.*, 2013). By identifying which patients will respond to drugs before drug treatment, patients will have reduced exposure to adverse events and will be able to identify effective therapies quickly without long ''trial runs'' in the clinic.

There are currently no known universally effective drug therapies for alopecia areata. However, there is emerging convergence of genetic characterization of alopecia areata patients substantiating distinct genetic subclasses of patients—with patients phenotypically expressing alopecia universalis and alopecia totalis having stronger genetic association with disease and variation in the *ULBP* (cytomegalovirus UL16-binding protein) gene cluster on chromosome 6q25.1 (Petukhova and Duvic, 2010).

As understanding of genetic influence for the development of disease progresses, new molecular targets for drug therapy will be identified. By using pharmacogenetic assessment of patients participating in clinical drug trials for alopecia areata, researchers will begin to learn which patients respond more readily to drug therapies and which patients may be predisposed to toxicity with particular drug therapies. Furthermore, stratification of clinical trials by genetic subgroup rather than phenotypic subtype of alopecia areata will better characterize disease subpopulations and help determine scientifically guided approaches to drug classes that will impact specific disease mechanism pathways.

Because clinical trials for alopecia are often small with limited longitudinal follow-up, it is imperative that patient genetic samples with broad consent for ongoing research be collected during clinical trials. In addition, uniform characterization of clinical phenotype and response across clinical trials must be considered in order to pool patient responses to therapy for genetic research. This will enable genetic studies to link to uniform clinical response data sets in order to better characterize genetic association with clinical response. Patient advocacy organizations like the National Alopecia Areata Foundation will be critical in bringing researchers from academia and industry together to create large enough research data sets to determine best approaches for therapy.

Additionally, characterizing the lifetime disease burden for patients with different genetic subtypes of disease will influence overall approach to therapy. For example, cosmetic treatment of hair loss may be only a portion of the overall treatment goal for these patients. Systemic therapies may prove more effective to prevent or delay additional complications of this autoimmune disease.

This information will translate into individualized medical practice for patients with alopecia areata. Researchers will learn how patients with alopecia universalis and alopecia totalis respond differentially from patients with classic alopecia areata to available drug therapies and create algorithm-based approaches to drug therapy. For drugs with known toxicities, genetic tests may be made available to assess individual patient risk for adverse events before starting treatment. By assessing risk, alternative drugs or doses of drugs can be considered. This is especially important for alopecia areata, which is a chronic autoimmune disease with a substantial portion of patients experiencing initial presentation in childhood.

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CONFLICT OF INTEREST

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